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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/692,330	10/22/2003	Stuart Tugendreich	03916.0003.NPUS00	8575

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EXAMINER	
MCGILLEM, LAURA L	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 10/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/692,330	TUGENDREICH ET AL.	
	Examiner	Art Unit	
	Laura McGillem	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) *4 and 5* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 6-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

It is noted that claims 1 and 6 have been amended and claim 8 has been added in the amendment filed 7/6/2006. Claims 1-3 and 6-8 are under examination.

Claim Rejections - 35 USC § 112

Claims 1 and 6 have been amended to remove indefinite phrases . The rejection of claims 1-3 and 6-7 under 35 USC 112, second paragraph from the Office Action mailed 1/25/2006 have been withdrawn. However, upon further consideration, a new ground(s) of rejection is made below.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3 and 6-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite because it recites the phrase "an effective amount" in part a) and the metes and bound of what would constitute an "an effective amount" to cause depletion of reticulocytes in a subject are not clear. The skilled artisan would not know what amount of a test compound that the Applicants intend to be administered in order to be effective.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 and 6-8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation *United States v. Telectronics*, Inc., 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is required is not based upon a single factor, but rather is a conclusion reached by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and include the following:

1) Scope of the claims. The claims are drawn to a method for determining the propensity of a test compound from a group of compounds known to cause depletion of reticulocytes, to cause depletion of reticulocytes in a subject. By determining the statistical significance in the change in expression level of indicator genes in response to the compound, a probability of reticulocytes depletion can be assigned to the compound. The specification discloses that a test compound known to cause reticulocyte depletion can comprise small organic molecules, drugs, prospective

pharmaceutical lead compounds, proteins, peptides, polynucleotides, heterologous genes, plasmids, polynucleotide analogs, peptide analogs, lipids, carbohydrates, viruses and phage, parasites that are known to cause reticulocyte depletion, which encompasses a very large group of compounds. The indicator genes to be used can be in a Reticulocyte Depletion Signature. The specification discloses that a Group Signature typically comprises about 2 to about 50 gene identifiers of varying degrees of specificity, but at other times signatures of length 100, 500 or even all genes present in a detection array may be desirable. The specification discloses that a gene identified in a signature also includes homologs and orthologs. Therefore, the number of a "plurality of indicator genes" encompasses a very large group of possible indicator genes. The claims are drawn to depletion of reticulocytes in a test subject. The scope of a test subject encompasses a very large group, including a biological organism, cell, tissue, or a model of a biological system capable of reacting to the presence of a test compound, typically a prokaryotic organism, eukaryotic cell or tissue sample or a live animal including, without limitation, human, monkey, rat, mouse, cow, sheep, dog, cat, chicken, pig or goat. The specification discloses that the eukaryotic subjects can be tested *in vivo* or *in vitro*. The scope of the claimed method also comprises determining expression in any cell type in any subject, which encompasses a very large group of sources of indicator genes in a test subject including cells from organs which are not related to reticulocyte production or depletion.

2) State of the Art. In a review of the predictive value of *in vitro* toxicity models, Davila et al (Ann. Rev. Pharm. Toxicol., 1998, Vol. 38 Pages 63-96) teaches that before

in vitro findings can be correlated with *in vivo* human toxicity, certain basic steps should be followed such as: identify the appropriate target organ and species, develop and characterize a suitable *in vitro* system, perform toxicity studies with model test compounds and reasonable *in vitro* concentrations and exposure times, employ a battery of cytotoxic assays to evaluate the compounds, after the evaluation of the model compounds, measure the toxicity of unknown agents, compare and contrast their toxicity with model compounds and examine the mechanism of toxicity with more detailed and in depth investigations. Lastly, Davila et al recommend the step of conducting interlaboratory validation studies (see page 64, Table 1, for example). Davila et al teach that unknown or untested compounds can be evaluated with an *in vitro* model system after thorough examination of the model compounds to demonstrate the validity and sensitivity of the *in vitro* system to detect known toxic compounds (see page 64, last paragraph bridging to page 65, 1st paragraph, for example). Therefore Davila et al teach that careful experimentation is required to establish that the endpoint measured in the *in vitro* model system can be reliably correlated with a given *in vivo* toxicity, before data obtained *in vitro* can be used to predict the toxic properties of a compound.

3) Unpredictability of the art. The unpredictability of whether the propensity of test compounds to deplete reticulocytes can be determined based on changes in gene expression is manifested in the correlation between changes in gene expression and depletion of reticulocytes. In an article published close to the effective filing date of the instant application, Waring et al (Curr. Opin. Mol. Ther. Jun 2002, Vol. 4, No.3, pages 229-35) teach the unpredictability of *in vitro* predictive systems particularly with respect

to toxicogenomic methods. Waring et al states that it is "too early to determine if gene expression markers for toxicity can be extrapolated from cell culture to animal systems" and "a great deal of additional research will be required in order to consistently link the changes seen *in vivo* and *in vitro*" (see page 233, left column, 2nd paragraph, for example). The assertions of Waring et al are based in part on the observation that fifteen well-characterized hepatotoxins grouped together differently and gave very different expression profiles in isolated rat hepatocytes versus treated rats. Waring et al teach that the question that remains to be addressed is whether gene expression alone is enough to predict and/or identify a mechanism of toxicity, including how great an effect time points and concentrations will have on the overall expression profile and the ability of microarray analysis to identify cell-specific toxicity (see page 233, left column, 3rd paragraph, for example). The teachings of Waring et al indicate that the validity of *in vitro* toxicogenomic models for toxicity is at least as unpredictable as other systems and as described by Davila et al, requires careful empirical verification to establish the predictive capabilities of the model system.

Thomas et al (2002, Toxicogenomics, pages 31-38, Eds. Inoue and Pennie) teach that the correlative value of any particular toxicogenomic method is unpredictable. Specifically Thomas et al teach that "just identifying the disrupted pathways and associated gene expression changes do not necessarily provide a method to predict similar toxic responses with other chemicals or across species. A big challenge for the emerging field of toxicogenomics will be to develop models and tools that use gene expression measurements to ultimately predict toxicity in untested chemicals and also

determine whether a similar toxic response will occur in humans" (see page 32, 2nd paragraph, for example). Therefore, Thomas et al teach that developing models and tools that use gene expression measurements to predict toxicity in untested compounds remained a challenge to be overcome in late 2002, and thus was clearly not routine when the instant application was filed.

Thomas et al teach that there are two important points concerning development of predictive toxicological models using gene expression: the information contained within the predictor variables and selection of a diagnostic subset of genes (see page 34, 1st paragraph, for example). Thomas et al teach that the classification of a chemical set into a toxicological class or endpoint based on gene expression is difficult due to the variety of potential mechanisms that underlie the toxicity of these chemicals and discloses examples of compounds that arrive at the same toxic endpoint by distinct pathways (see page 34, for example). Thomas et al teach that interpreting toxicogenomic data is also complicated by the fact that "multiple factors converge to ultimately influence the manifestation of toxicity and associated gene expression system patterns" (see pages 34-35 bridging paragraph, for example). It is reasonable to assume that because factors such as time, dose, route of administration, age and sex would create even greater uncertainty in using findings obtained in such a system to predict the likelihood of whether a test compound is toxic and how toxic it would be compared to other compounds. Thus, the teachings from the art clearly establish that at the time of filing, the skilled artisan would not be able to predict toxicity of a test compound on reticulocytes based on data obtained from the claimed gene expression

assay without first establishing a correlation between claimed model system and method and the relevant *in vivo* system. The skilled artisan would have to rely on the teaching of the instant disclosure for the manner and process of performing the claimed method for determining whether selected test compounds cause depletion of reticulocytes based on alterations in expression of a few indicator genes. The teaching of the instant specification must be set forth in such clear concise and exact terms as to enable the skilled artisan to practice the invention without undue experimentation.

4) Amount of guidance provided. The specification provides some guidance on the dosage of a test compounds that would be used in the claimed methods. The specification discloses that compound dosing was based on the acute dose LD_{50} recorded in published references or literature sources. The maximum tolerated dose (MTD) and the fully effective dose (FED) can be determined for a compound. The specification discloses that the MTD or FED of test compounds were administered to a small population of rats using various methods of administration. Applicants disclose that various tissues were harvested and used to prepare mRNA for microarray testing. Applicants disclose that genes that exhibited the greatest variability in expression level during a large number of test treatments encompassing 10 to more than 100 compound treatments were selected from the datasets of several hundred or more genes. Applicants disclose that only a few genes responded to a high degree and 100-500 exhibit a lesser but still substantial response. Applicants teach that the maximum number of compounds that can be included in the experimental group is preferably limited to no more than 200 compounds.

5) Working examples. The specification provides a working example of the method to produce a Reticulocyte Depletion Signature identifying drug treatments that cause damage to an organism in a way that resembles the toxicity caused by chronic or acute overdose of anti-neoplastic or immunosuppressant compounds. The specification teaches that the Reticulocyte Depletion Signature was derived by analysis of a subset of data using about 300 individual drugs representing multiple tissues. In this example, the expression data subset used for analysis was from the livers of rats treated with compounds that significantly decreased the signal intensity for two specific reticulocyte-enriched transcripts, as compared with vehicle-treated control animals. The example compounds were hydroxyurea, cytarabine, doxorubicin, ifosfamide, thioguanine, azathioprine, etoposide, and albendazole. The specification discloses dosages used for each compound and method of administration. The specification teaches that only two indicator genes (aminolevulinate synthase 2 and peripherin) were used in the exemplified method based on their high expression levels in reticulocytes and detectable response to drugs with known bone marrow toxicity. Table 2 illustrates calculated data for aminolevulinate synthase 2 and peripherin based on gene expression changes. Table 3 illustrates the validation analysis of the depletion signature using 20 partitions of a standard data set. Table 4 shows the generated Signature Projection Scores for ~38 compounds using data from liver and ~33 compounds using data from bone marrow and spleen. The Signature Projection Scores were characterized by comparing it with all the compound gene expression data in the Drug Matrix database.

6) Nature of the invention. The nature of the invention involves predicting the propensity of a test compound to deplete reticulocytes in a subject based a probability calculated by the effect of the compound on gene expression levels, which is an aspect of toxicogenomics, a complex and unpredictable aspect of science and medicine. The calculation of the signature projection score appears to be a modification of current statistical methods such as the correlation coefficient method, which as a newly proposed quantitative approach in statistics and genomics would need to be extensively validated.

7) Level of skill in the art. The level of skill in the art is high, but given the scope of the claims, the guidance and example provided, the state of the art and unpredictability of the art, the skilled artisan would have had to have practiced undue empirical experimentation in order to determine the propensity of test compounds to deplete reticulocytes based on changes in gene expression. Given the above analysis of the factors which the Courts have determined are critical in ascertaining whether a claimed invention is enabled, it must be considered that the skilled artisan would have had to have practiced undue and excessive experimentation in order to practice the claimed invention.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura McGillem whose telephone number is (571) 272-8783. The examiner can normally be reached on M-F 8:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Laura McGillem, PhD
10/2/2006

DANIEL M. SULLIVAN
PATENT EXAMINER